Clinical Commentary

Prevention of perinatal group B streptococcal infection: Current controversies

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Group B streptococcus (GBS) is the most frequent cause of neonatal sepsis in the United States. The Centers for Disease Control and Prevention (CDC) issued guidelines for its prevention in 1996. This article details areas of controversy with those guidelines and offers recommendations for resolution. We recommend that a prevention policy be adopted by all hospitals. If a screening-based policy is chosen, compliance is essential. Penicillin is the antibiotic of choice for GBS prevention. Increasing resistance to clindamycin and erythromycin might eliminate them as alternative choices in patients allergic to penicillin. Group B streptococcal prophylaxis might not be necessary in women who have repeat elective cesarean delivery. In asymptomatic women, a positive urine culture for GBS should be considered clinically equivalent to a positive vaginal or rectal sample for screening. Neonatal sepsis caused by organisms other than GBS must be monitored carefully by all hospitals providing obstetrics services. (Obstet Gynecol 2000;96:141–5. © 2000 by The American College of Obstetricians and Gynecologists.)

Group B streptococcus (GBS) first emerged as an important pathogen in the 1970s, and since then has remained the major cause of sepsis in newborns.[1] Studies indicate that 10–30% of pregnant women are colonized with GBS in the gastrointestinal or genital tracts.[2] These women have the potential for transmitting this organism to their newborn infants vertically or, rarely, by hematogenous dissemination. Because colonized women have no symptoms of disease, a culture is required to diagnose the presence of the organism in the vaginal or rectal area.

Because of pressure to implement programs to decrease the prevalence of GBS sepsis in the perinatal period, the Centers for Disease Control and Prevention (CDC) prepared draft guidelines for prevention of disease in December 1994, followed by a consensus conference. Several organizations, including the ACOG, the American Academy of Pediatrics, and the Infectious Diseases Society for Obstetrics and Gynecology, provided input for these proposed guidelines for prevention. In 1996, the guidelines were published in the CDC Morbidity and Mortality Weekly Report with options for the practicing physician to choose to screen pregnant women with vaginal or rectal cultures for GBS or to use clinical risk factors to determine whether a patient needed treatment during labor.[3]

With the screening-based approach, women who previously had a GBS-infected infant or had GBS bacteriuria during the current pregnancy or who have preterm labor should receive antibiotics during labor or after rupture of the membranes. For all other women, a vaginal or rectal culture should be done at 35–37 weeks. All women with a positive culture should be given intrapartum antibiotics as early in labor as possible. For women with a negative culture, prophylaxis against GBS is not recommended.

The risk-based approach eliminates screening cultures for GBS. Intrapartum antibiotics are given in the presence of any of the following risk factors: preterm delivery, rupture of membranes 18 hours or longer, intrapartum fever of greater than or equal to 38C (100.4F), a previous infant with GBS disease, or GBS bacteriuria during the current pregnancy.

Areas of concern have accompanied the institution of these guidelines. What are areas of potential noncompliance with the recommendations? What are the current limitations of the policy? Are the recommended antibiotics appropriate? Will bacteria become resistant to the antibiotics used for prophylaxis? How should women with preterm labor or preterm premature rupture of membranes (PROM) who do not deliver be treated regarding antibiotic administration? Should women who have elective cesarean delivery receive antepartum or intrapartum antibiotics, and if so, for what duration before delivery? The Infectious Diseases Society for Obstetrics and Gynecology asked us to attempt to answer these questions. (Dr. Schuchat rep-

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The CDC guidelines advise the practitioner to obtain cultures at 35–37 weeks' gestation for the best prediction of colonization status at delivery. Yancey et al[4] evaluated a comprehensive GBS treatment strategy involving over 800 women. The sensitivity of antenatal culture 6 or more weeks before delivery for identifying colonization status at delivery was 43% and the specificity was 85%. When cultures were obtained between 1 and 5 weeks before delivery, the sensitivity was 87% and the specificity was 97%. When cultures are obtained more than 5 weeks before delivery, there is a much greater chance that the results will not accurately predict colonization status at delivery.

The culture site and method are important aspects of the CDC guidelines. By combining vaginal and rectal cultures, the recovery rate of GBS is increased by 25% or more.[5] When clinicians do not follow these guidelines, they miss at least one fourth of patients whose cultures are positive for GBS and who might benefit from antibiotic prophylaxis. Many laboratories streak a blood agar plate with the swab, incubate it for 24 hours, and discard it if no growth of GBS is identified. Instead, the guidelines recommend the use of selective broth medium, an enriched medium that enhances the growth of GBS better than agar media, and is supplemented with antibiotics to inhibit the growth of organisms other than GBS.[3] When selective medium is used, there is a 50% higher rate of GBS isolation.[5] Most institutions use a nonselective transport medium (such as Amies medium) to transport rectovaginal swabs to the laboratory. It has been hypothesized that use of such media might result in a decreased yield of positive cultures.

The proper choice of antibiotic is important in successful disease prevention. The CDC guidelines recommend penicillin G as the first choice, with ampicillin as second choice. If the patient is allergic to penicillin, CDC suggests using clindamycin or erythromycin parenterally.[5] Group B streptococci are universally sensitive to the penicillins, and with its narrower spectrum, aqueous penicillin G is the drug of choice. As the interval between the first dose of penicillin and birth increases, the proportion of GBS-positive infants delivered from GBS-colonized mothers decreases. When antibiotics were given within 1 hour of delivery, 46% of infants were colonized, a rate similar to that of infants of untreated mothers. When the interval was 2–4 hours, 2.9% of infants were colonized with GBS. Only 1.2% of infants whose mothers received a first dose more than 4 hours before delivery were colonized.[6] The opportunity to prevent GBS transmission to the infant is greater when antibiotic prophylaxis is started early in the intrapartum period. We strongly endorse use of vaginal or rectal cultures, the use of selective broth media, and the choice of penicillin as the first-line antibiotic for intrapartum GBS prophylaxis.

A major concern regarding potential noncompliance pertains to failure to adhere to the policy guidelines, even when such a policy is in place in an institution. It is estimated that in 10–20% of cases there is, in fact, noncompliance. This is unavoidable in some cases because patients might refuse antibiotics or deliver precipitously (before antibiotics can be administered).[7] In other cases, patients might just barely meet the criteria (such as being within a few minutes of the time duration for membrane rupture or within a few days of being term when they deliver). In one study, the overall noncompliance was 19.7%, but nearly half of those protocol deviations resulted from factors beyond the control of the physician or constituted marginal situations, as mentioned above. The remaining half resulted from an error or omission by the staff.[7] It is possible that better compliance might be achieved with a dedicated effort on the part of physicians, nurses, and ancillary personnel.

To improve compliance with this protocol, hospitals are encouraged to heighten the index of suspicion of clinicians. This can be accomplished by placing special labels on a woman's chart or by instituting a reminder to practitioners on the labor and delivery board as to when a woman becomes at risk. Standing orders might also help ensure that women with appropriate criteria are offered intrapartum antibiotics.

Several persisting clinical treatment questions must be addressed. Should chemoprophylaxis for GBS be given to women who have elective cesarean delivery? This has proved to be an important practical question. The current guidelines state only that intrapartum antibiotics should be given and thus provide no specific recommendations for women admitted for elective cesarean delivery. In addressing this question, one must consider both the risk of sepsis to the newborn delivered to a colonized mother and the number of additional maternal-neonatal exposures to antibiotics. The risk of sepsis to the newborn in this situation is estimated to be low. The number of additional antibiotic exposures is estimated to be in the range of 1% of the total population (assuming that 20% of the population is colonized and the total rate of cesarean delivery for patients with no labor and no ruptured membranes would be approximately 5% of the total obstetric population [approximately 25% of the total number of cesareans]).

Recognizing that an interval of at least 4 hours from the beginning of prophylaxis to delivery is ideal, one might argue that prophylaxis in the setting of a cesarean without labor or ruptured membranes should be given

4 hours before delivery. However, because many patients are admitted on the morning of such an elective, scheduled cesarean delivery, a requirement of the patient getting 4 hours of prophylaxis before delivery would mean a considerable inconvenience to patient and staff. This would require the patient to be admitted by at least 3:00 to 3:30 AM for a delivery scheduled for 8:00 AM.

It has been shown recently that vertical transmission of GBS is decreased markedly with 2–4 hours of prophylaxis.[6] One possible solution would be to administer the antibiotics 2 hours before the cesarean to achieve some benefit. Another option would be to schedule the cesarean for a time more than 4 hours after the antibiotic was administered. Data recently presented by Ramus et al (Ramus RM, McIntire DD, Wendel GD. Antibiotic chemoprophylaxis for group B streptococci is not necessary in elective cesarean section at term [abstract]. Society for Perinatal Obstetricians, San Francisco, CA, 1998, #277) suggest that chemoprophylaxis is not necessary in elective cesarean delivery at term. From 1988–1997, the authors identified 3546 patients who met criteria for inclusion in their study. Patients in labor with cervical dilatation over 4 cm, ruptured membranes, or at less than 37 weeks' gestation were excluded from the study. No patients received preoperative antibiotics. None of the 3590 infants were infected with GBS. Using the colonization rate in their population, the authors expected 539 (15%) of the women who had elective cesarean delivery to be GBS carriers. The observed attack rate in presumably colonized women was 0% (95% confidence interval CI 0.0, 0.7%). It is of note that the upper limit of the 95% CI (0.7%) is close to the overall attack rate of infants born to colonized women (1%).

How should we treat women with preterm PROM without labor? The 1996 guidelines recommend that a GBS culture be collected, and then either antibiotics should be given until the culture returns with a negative result or once a positive culture result is available. There are several important related issues that must be considered.

If the initial culture for GBS is negative, should the culture be repeated; if so, when? The likelihood that a negative antenatal culture will become positive in the 5 weeks after it was obtained is 5%.[4] Therefore, we believe that it is not necessary to repeat a negative culture for up to 5 weeks. If the initial culture is negative, should prophylaxis be given when the woman does go into labor in the preterm period? There are no data on which to base answers to that question. Again, it is unlikely that the woman would have become colonized. The 1996 CDC guidelines recommend the administration of antibiotics only to women with positive or unknown culture results.

If the initial culture is positive, how long should antibiotics be given? Data are not available upon which we can base a recommendation for this situation. This is antibiotic prophylaxis; therefore, we recommend administering antibiotics for 48 hours and then obtaining a second culture while the patient is taking antibiotics to determine whether colonization was suppressed. Antibiotics are continued until culture results are received. If the culture is still positive, intravenous antibiotics should be given for an additional 5–7 days. If the culture is negative, the antibiotic should be discontinued. Any patient with a positive culture should still receive intrapartum antibiotics.

What is the best way to treat a woman with preterm labor that was arrested with tocolytics? The 1996 guidelines indicate that such women should receive intrapartum antibiotics for GBS prevention, but make no other suggestions. If labor ensues within 5 weeks, the original culture is sufficient; if labor occurs after 5 weeks, a repeat culture should be obtained.

Is there a threshold colony count for treating GBS bacteriuria? Infants born to mothers who are heavily colonized with GBS are more likely to become colonized than are infants whose mothers are lightly colonized. Regan et al[8] demonstrated that the odds of infection were 2.54 times greater in infants born to heavily colonized mothers compared with lightly colonized mothers.

Infants born to mothers with GBS bacteriuria during pregnancy are more frequently and more heavily colonized with GBS.[9] In addition, these infants are at increased risk for invasive GBS disease. In the only prospective study that provided data comparing attack rates of GBS infection in infants born to mothers with or without GBS bacteriuria, Moller et al[10] found a 2.5% prevalence of GBS bacteriuria in pregnant women screened between 12 and 38 weeks. There were five cases (7.35%) of confirmed GBS sepsis among 68 infants born to women with GBS bacteriuria compared with zero cases among 2677 women without bacteriuria ($P < .001$). Persson et al[9] reported one infant with GBS disease among ten born to women with GBS bacteriuria levels over 10^5 CFU/mL. Six of those women, excluding the mother of the infected infant, received antepartum antibiotics. Although the number of reported cases is limited, the observation that eight of 92 infants born to mothers with GBS bacteriuria developed GBS infection suggests an attack rate of 87 (95% CI 51, 101) per 1000 live births.

Any GBS-positive urine culture is a marker for genital tract colonization, and the woman should receive intrapartum antibiotics as if she had positive vaginal or

rectal results. A subsequent culture of the vagina and rectum is not recommended in patients who have had a positive urine culture for GBS because a negative culture could be a false-negative test. We recommend treating symptomatic and asymptomatic GBS urinary tract infections in pregnancy according to current standards for care.

If a patient has a negative GBS screening culture at 35–37 weeks, should prophylaxis be given with rupture of the membranes longer than 18 hours? There are no data on which to base a recommendation for this clinical situation. It is unlikely that a negative culture at 35 weeks would become positive at term, and although there is increased risk of maternal infection with prolonged rupture of membranes, the current guidelines do not recommend the use of antibiotics unless the patient has clinical signs of infection. We agree that the low risk of infection does not warrant antibiotics for the purpose of GBS prevention in this situation.

There are other limitations to current prevention approaches. Such approaches do not prevent all early-onset disease; some cases will continue to occur despite prophylaxis or in women who are identified as not needing prophylaxis. Even in the best-case scenario, not all women who are at risk will be detected. In addition, the current approaches might not have a measurable effect on late-onset disease and will have no effect on other syndromes possibly caused by GBS (such as premature delivery, stillbirth, or disease in nonpregnant adults).

Both the screening-based and the risk-based approaches provide antibiotics during labor and delivery to a large proportion of women (approximately 15–25% of parturients, or an increase of 10–20% more than would otherwise receive antibiotics during labor).[11] Antibiotics can have adverse effects, including mild allergic reactions, anaphylaxis, or selection of antimicrobial-resistant pathogens. Therefore, the substantial increase in use of antibiotics for preventive purposes must be considered with respect to the magnitude of unintended consequences. Increased use of antibiotics during labor can also have consequences for newborn treatment; recent pediatric recommendations suggest a 48-hour observation period for infants whose mothers received antibiotics. This practice might be prudent from a clinical perspective, but it has cost implications for hospitals and insurance companies in areas that routinely discharge infants in less than 48 hours.

In addition to these general limitations to the use of intrapartum antimicrobial prophylaxis, the consensus screening-based and risk-based approaches have some limitations specific to their protocols. The screening-based approach is implemented most efficiently when information on the prenatal culture result is consistently available to clinicians at the time of labor and delivery. This information might not be available if a woman did not have prenatal care, was not screened during prenatal care, or had a screening test for which results are pending or are not available at the delivery facility. In circumstances in which prenatal culture results are not available, the decision to use intrapartum antimicrobial prophylaxis should be made on the basis of the presence of one of the clinical risk factors for early-onset disease.

The risk-based approach does not require prenatal specimen collection or information transfer because the only prenatal component of this approach is the recommendation that women be advised of the prevention strategy available to them. The major limitation of the risk-based approach is that asymptomatic colonized women at term are not identified. Antimicrobial prophylaxis would not be offered to these women, and this approach cannot prevent the proportion of cases that occur in the infants of such women. It is estimated that 30–50% of the cases of early-onset GBS sepsis develop in infants born to women without risk factors.[12]

Perhaps the most important policy issue involves this critical question: is invasive GBS infection decreasing in neonates? Surveillance data from individual hospitals[7] and larger populations such as the CDC's multistate surveillance areas[13] showed decreasing rates of early-onset GBS disease even before publication of the 1996 guidelines. Rates are lower in geographic areas where more hospitals have prevention policies,[11] which leads us to encourage all hospitals to adopt a GBS prevention policy.

The choice of treatment among patients allergic to penicillin is important. The CDC guidelines recommend clindamycin or erythromycin. Recent data indicate that 15% of GBS isolates are resistant to clindamycin[14] and 21% to erythromycin.[15] These data indicate that infants born to mothers who receive clindamycin or erythromycin should be carefully evaluated for sepsis. We recommend that sensitivity testing for erythromycin and clindamycin be done on all GBS-positive isolates obtained from women who have a history of adverse reaction to penicillin. Although cephalosporins are not listed in the CDC guidelines, a first-generation cephalosporin might be an acceptable choice for women allergic to penicillin without a history of anaphylaxis, because GBS resistance to cephalosporins has not been identified.

Of greater concern is whether intrapartum use of broad-spectrum ampicillin affects the incidence and the resistance of early-onset neonatal sepsis with organisms other than GBS. Recently, Towers et al[16] evaluated the increased administration of antenatal ampicillin to pregnant women for GBS prophylaxis. Over 6 years, 42 cases of early-onset neonatal sepsis were detected among 29,897 infants delivered. There were 15 cases of GBS sepsis and 27 non-GBS cases. Twenty-one of the non-GBS cases involved gram-negative rods, and six

Table 1. Recommendations for GBS Prevention*

Every hospital in the United States should adopt either a screening-based or a risk-based GBS prevention policy. A (II)
Use selective broth media for GBS cultures. A (II)
GBS screening cultures should sample both the lower vagina and rectum. A (II)
Use penicillin as the antibiotic of choice for GBS prophylaxis. A (I)
Among penicillin-allergic patients, clindamycin and erythromycin might not be the best alternative agents because of unacceptably high rates of resistance. A (II) Use an appropriate spectrum cephalosporin if there is no history of immediate hypersensitivity to penicillin. C (III)
If the mother has chorioamnionitis, use a single, broad-spectrum antibiotic or ampicillin plus gentamicin. Clindamycin should be added if a cesarean delivery is required. A (I)
Do not use antibiotic prophylaxis for women undergoing elective cesarean delivery. If used, the dose can be given pre-incision. B (II)
In asymptomatic women, consider a positive urine culture the same as a positive genital tract screen in determining the need for intrapartum prophylaxis. In addition, treat women with a urine culture positive for GBS antepartum when the diagnosis is made. A (II)
Because there is an increased risk of non-GBS sepsis among infants whose mothers received ampicillin, strongly consider establishing surveillance for neonatal sepsis by resistant organisms. B (II)
Intravenous intrapartum antibiotic prophylaxis is currently the best method for decreasing the incidence of GBS sepsis in newborns. A (II)

GBS = group B streptococcus.

* Recommendations are rated using the Evidence-Based Medicine Working Group guidelines.

involved gram-positive cocci. Among these 27 cases, 15 women had received ampicillin, and 13 of the 15 bacterial isolates (87%) were resistant to ampicillin. Among the 12 cases in which no antenatal antibiotics were administered, only two (17%) had ampicillin-resistant isolates.[16] These data support the use of penicillin rather than ampicillin as the antibiotic of choice in GBS prophylaxis.

Among women who have a history of hives or anaphylaxis to penicillin, we recommend that susceptibility testing to clindamycin and erythromycin be requested for any positive GBS culture. If the organism is resistant, vancomycin would be a better choice than a cephalosporin. Table 1 presents the recommendations of our group using the Evidence-Based Medicine Working Group guidelines.[17]

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